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Original article

Concurrent Radiochemotherapy in Locally Advanced Head and Neck Cancer: Analysis of Treatment Results and Prognostic Factors

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Background and Aim: The prognosis of patients with locally advanced head and neck cancer is generally poor. By understanding the prognostic factors, treatment of individual patients may be optimized. The aim of this study was to evaluate the treatment outcomes and different prognostic factors affecting survival in patients with advanced head and neck squamous cell carcinoma (HNSCC).
Patients and Methods: Data of patients with locally advanced HNSCC who received radiochemotherapy (RCT) including conventional radiotherapy (66 -70 Gy/33 -35 fractions) plus concurrent weekly cisplatin (30mg/m^2) between April 2005 and December 2008 were retrospectively analyzed. The relation between eight potential prognostic factors and survival was explored.
Results: Sixty patients were eligible for the analyses. Complete response was achieved in 23 (38%) patients and partial response in 16 (27%). The median follow- up period was 23 months (95% CI, 19.2 - 26.8). The median progression-free survival and overall survival were 16 and 25 months, respectively. Acute grade 3 mucositis was seen in 18 (30%) patients. Late toxicities of larynx and esophagus were observed in 6 (10%) and 4 (7%) patients respectively. Factors associated with poorer overall survival were poorly differentiated histology (p<0.001), advanced T stage (p<0.01), advanced N stage (p<0.001), higher overall stage (p<0.001), hypopharyngeal primary tumor site (p=0.01) and treatment interruptions (p<0.001).
Conclusion: Concurrent RCT with weekly cisplatin may be an effective treatment for locally advanced HNSCC in a resource-limited setting. It appears important to avoid radiotherapy interruption to improve outcome in patients with locally advanced HNSCC.

Key words: Head And Neck Cancer, Radio-Chemotherapy, Prognostic Factors, Weekly Cisplatin
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INTRODUCTION

Head and neck cancer incidence is increasing in many parts of the world and it accounts for 3% of cancer cases worldwide[1].

In Egypt, the incidence of head and neck cancer of both sexes in 2012 was as follow: Lip and oral cavity 1687 cases (1.6%), nasopharynx 263 (.2%), other pharynx 553 (.5%) and larynx 1472 (1.4%). The mortality rate for lip and oral cavity was 659 cases (.9%), nasopharynx 142 (.2%), other pharynx 423 (.6%) and larynx 652 (.9%) were reported[2].

For a long time, and before the introduction of radiochemotherpay (RCT) approach, radiotherapy has been one of the treatment options for respectable head and neck squamous cell carcinoma (HNSCC) and the main line of management for advanced stage HNSCC[3]. The emergence of concomitant platinum-based RCT as a standard treatment for locally advanced HNSCC is based on the strong evidence supporting its role in improving locoregional control and survival when compared to radiotherapy alone[4, 5]. One of the chemotherapy administration schedules during RCT for HNSCC is to give cisplatin every 3 weeks[6]. Another schedule is to administer cisplatin on weekly basis. The weekly administration of cisplatin is widely utilized based on the hypothesis that the weekly administration would provide better radiosensitization and less morbidity [8, 9].

It is unfortunate that patients with locally advanced HNSCC have a poor prognosis in general. Understanding the factors that influence prognosis in this group of patients may be helpful in tailoring optimum care for individual patients[10]. A number of prognostic factors that correlates with survival in advanced HNSCC have been identified. These factors included, for example, pre-hemoglobin level, interruption of radiotherapy treatment, performance status, histological grade and tumor stage[10, 11].

The objective of this study was to analyze the results of RCT treatment using radiotherapy plus concurrent

weekly cisplatin in Egyptian patients with HNSCC, as well as to identify the influence of various patient and tumor-related prognostic factors on survival in these patients.

PATIENTS AND METHODS

Treatment plan

The medical records of all patients with head and neck cancer who presented to the Clinical Oncology Department - Assiut University Hospital between April 2005 and December 2008 were retrospectively reviewed. The study protocol was approved by the ethics committee of Assiut University, Egypt.

Eligibility criteria

Eligible patients were those with biopsy-proven HNSCC, stage III or IV according to the American Joint Committee on Cancer (AJCC) [12] staging system with no distant metastases. All anatomic sites of the head and neck were included except nasopharyngeal carcinoma.

Exclusion criteria included patients treated with neoadjuvant or adjuvant chemotherapy or unconventional radiotherapy.

Radiotherapy

Treatment was delivered with either cobalt teletherapy or a linear accelerator machine (4 or 6 MV). Patients were treated using conventional two-dimensional radiotherapy which was planed using simulator after immobilization with thermoplastic mask and treated with shrinking field technique. All patients were treated with bilateral opposing portals to the primary sites and upper neck nodes level II and III. For patients who had lymph node metastases, the lower neck region (level IV) and supraclavicular fosse were irradiated with a total dose of 50 Gy using an anterior single port and electron beams were used to boost the dose delivered to the posterior cervical lymph nodes. Spinal cord shielding was applied after 40 Gy in 20 fractions. The prescribed dose to the primary lesion and the involved nodal disease was 66-70 Gy in 3335- fractions over 6.5- 7 weeks. Uninvolved areas were electively treated with a total dose of 50Gy over 5 weeks. All the fractions were given as 2Gy per fraction, one fraction per day, 5 fractions per week.

Chemotherapy

Cisplatin 30 mg/m^2 was administered within 2 hours before the radiation session as intravenous infusion over one hour on days 1, 8, 15, 22, 29 and 36 of the radiation schedule. Routine hydration with 500 ml normal saline given 30 -45 minutes before chemotherapy and 1000 ml of normal saline given over 2 hours immediately after chemotherapy was used. Patients received ondansetron plus dexamethasone given as intravenous bolus for antiemetic prophylaxis 30 minutes prior to chemotherapy. The cisplatin dose was modified on a case-by-case basis according to the level of leucopenia and/or thrombocytopenia, serum creatinine or liver dysfunction. In addition weekly cisplatin was altered to weekly carboplatin in some cases according to the toxicity.

Response assessment and follow-up

Patients were monitored weekly during the course of RCT to assess the response and the toxicity of therapy. Response to RCT was evaluated 4 -6 weeks after the completion of treatment and was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST)[13].

Acute toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTCAE v3)[14] and late toxicities were assessed using the Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Schema[15].

Patients were followed up monthly during the first year after treatment then every 3 months.

Study endpoints

The endpoints of the study were response to RCT, overall survival (OS), progression-free survival (PFS), acute and late toxicities and assessment of prognostic factors affecting OS. Variables assessed for their prognostic significance included age, sex, cigarette smoking (non-smokers vs. current smoking), subsite at the primary site (larynx vs. hypopharynx vs. oropharynx vs. oral cavity), T stage (T2 -3 vs. T4), N stage (N0-1 vs. N2- 3), overall stage (III vs. IV), histological differentiation (well vs. moderate vs. poor) and interruption during radiotherapy (yes vs. no). Treatment interruption was defined as stopping radiotherapy for >7 consecutive days.

Statistical analysis

PFS was calculated from the date of start of treatment to the first evidence of relapse, progression or death. OS was measured from the date of starting treatment to the date of death from any cause or the last date the patient was known to be alive. PFS, OS and

median follow-up were calculated using the method of Kaplan-Meier [16].

Data expressed as numbers, percentage, means and standard deviation. Prognostic factors affecting OS among cohorts were compared by using the Log-rank test for univariate analysis and Cox regression model for multivariate analysis. Statistical significance was defined as p-value less than 0.05. All statistical analysis was analyzed by computer program using SPSS 21.0 (SPSS, Inc. Chicago, IL).

RESULTS

Sixty patients who were planned for definitive concurrent CRT with regular follow-up were identified as eligible for the study. The patients and tumor characteristics are shown in Table 1.

Response to treatment

Response to treatment is presented in Table 2.

All patients received the prescribed total radiotherapy dose which ranged from 66 to 70 Gy and 51 patients (85%) received seven cycles of concurrent cisplatin. Nine patients (15%) required greater than 7 weeks to complete the treatment with interruptions due to toxicity.

Relapsed patients received combination chemotherapy regimen in the form of cisplatin, 5-Fluorourcil ± docetaxel.

Survival

The median follow-up period was 23 months (95% Confidence Interval [CI]: 19.2- 26.8).

The median PFS was 16 months (95% CI: 12.6-19.4) and the median OS was 25 months (95% CI: 21.8-28.2).

Analysis of the prognostic factors

The impact of prognostic factors on OS by univariate analysis is summarized in Table 3.

The result of multivariate analysis is illustrated in Table 4.

Toxicity analysis

The acute adverse events, including hematological and non-hematological toxicities are showed in Table 5.

No episodes of febrile neutropenia were recorded. No grade 3 renal toxicity.

Toxicity of treatment leading to interruption of radiotherapy was seen in nine patients (15%).

Acute dysphagia occurred in 24 (40%) patients. Dysphagia gradually resolved with time but late swallowing dysfunction (grade II dysphagia) was observed in 4 (6.7%) patients and two of them needed esophageal dilatation two years after completion of treatment.

Grade I laryngeal toxicity in the form of hoarseness of voice was observed in 6 (10%) patients. Twelve (20%) patients complained of dry mouth during follow-up and nine (15%) patients had grade I skin changes. There was no aspiration pneumonia, cervical plexopathy and no case treated by laryngectomy.

Table 1: Patient and tumor characteristics

Characteristic	n.	%
Age		
Median (range)	50 (36-82)	
<50	15	25
>50	45	75
Sex		
Male	42	70
Female	18	30
Eastern Cooperative Oncology Group (ECOG) performance scale		
0	40	66.7
1	20	33.3
Smoking		
Never	19	31.7
Cigarette smoking	41	68.3
T stage		
T 2-3	43	71.7
T 4	17	28.3

N stage		
N 0-1	30	50
N 2-3	30	50
Stage		
III	26	43.3
IV	34	56.7
Histological differentiation		
Well	20	33.4
Moderate	24	40
Poor	16	26.7
Primary site		
Larynx	26	43.3
Hypopharynx	24	40
Oropharynx	10	16.7

Table 2: Clinical response of head and neck cancer patients in response to radiotherapy + weekly cisplatin

Primary site	**Response**			
	CR	**PR**	**SD**	**PD**
Larynx (n=26)	13 (50%)	8 (30.8%)	1 (3.8%)	4 (15.4%)
Hypopharynx (n=24)	5 (20.8%)	6 (25%)	6 (25%)	7 (29.2%)
Oropharynx (n=10)	5 (50%)	2 (20%)	2 (20%)	1 (10%)
Total (n=60)	23 (38.3%)	16 (26.7%)	9 (15%)	12 (20%)

CR= complete response, PR= partial response, SD= stable disease, PD= progressive disease

Table 3: Correlation between variables and overall survival in univariate analysis

Characteristic	**Mean ± SD**	**p value**
Age		
<50	35.93±21.75	0.362
>50	3/.86±17.72	
Sex		
Male	34./2±19.42	0.256
Female	27.82±17./5	
Smoking		
Never	30.42±18.50	0.614
Cigarette smoking	33.10±19.17	
Histological differentiation		
Well	42.36±16.65	<0.001
Moderate	38.00±16.07	
Poor	11.56±2.12	
T stage		
T 2-3	35.72±18.88	<0.01
T 4	22.87±15.67	
N stage		
N 0-1	44.93±15.35	<0.001
N 2-3	16.38±8.25	
Overall stage		
III	42.03±15.35	<0.001
IV	16.38±8.85	
Primary site		
Larynx	38.73±18.55	<0.02
Hypopharynx	24.08±16.16	
Oropharynx	34.10±19.93	
Radiotherapy interruption		
No	36.24±18.13	<0.001
Yes	12.60±4.16	

SD= standard deviation

Table 4: Correlation between variables and overall survival in multivariate analysis

Characteristic	Hazard ratio	p value
Histological differentiation		
Well, moderate or poorly differentiated	4.951	0.001
T stage		
T 2-3 or T4	1.603	0.104
N stage		
N 0-1 or N2-N3	2.372	0.011
Overall stage		
III or IV	1.681	0.083
Primary site		
Larynx, hypopharynx or oropharynx	1.024	0.468
Radiotherapy interruption		
No or yes	1.423	0.172

Table 5: Toxicity of radiotherapy and weekly cisplatin in the treatment of patients with locally advanced head and neck cancer

Toxicity	n.	%
Acute toxicity, grade III (NCI CTCAE v.3)		
Mucositis	18	30
Leucopenia	4	6.7
Nausea & vomiting	2	3.3
Late toxicity, grade II (RTOG/EORTC)		
Mucous membrane	12	20
Skin	9	15
Larynx	6	10
Esophagus	4	6.7

NCI-CTCAE v.3 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema

DISCUSSION

Two important goals of locally advanced HNSCC treatment are to control the disease and to preserve organ function. Concurrent RCT is an established approach to achieve these goals[17].

Cisplatin administered every 3 weeks at a dose of 100 mg/m^2 is an effective radiosensitizer in advanced HNSCC with significant DFS and OS benefit as proven in phase III randomized clinical trials[18]. However, the 3-weekly administration of cisplatin is associated with significant toxicities and low completion rate[18 -22].

When compared to the 3-weekly 100mg/m^2 cisplatin, the weekly cisplatin administration at a dose of 40mg/m^2 was more tolerable and associated with higher chemotherapy dose intensity[23]. Furthermore, the weekly administration of cisplatin as a radiosensitizer in advanced HNSCC has been shown to be effective in loco-regional disease control with an outcome comparable to that of the 3-weekly schedule[23, 25].

In the present study, concurrent RCT for locally advanced HNSCC using conventional radiotherapy and weekly cisplatin at a dose of 30mg/m^2 resulted in a 38% CR and the median PFS and median OS were 16 and 25 months, respectively.

Many studies assessed the efficacy of weekly cisplatin in doses ranging from 20 to 40 mg/m^2/week as a radiosensitizer in patients with HNSCC[8, 26- 29]. Gupta et al[8] retrospectively reviewed the results of treatment using radical radiotherapy (66 -70Gy) with concurrent weekly cisplatin (30 mg/m ^{2}) in patients with stage III and IV HNSCC and reported a 43% 5-years DFS rate.

In a prospective study, Homma et al [26] administered weekly cisplatin at higher dose of 40 mg/m^2 for 6 weeks with radiotherapy (70 Gy) and reported CR in 98% of patients and 2-years OS and PFS rates of 94% and 88% respectively. These results are higher than the results of the present study. The difference may be due to the inclusion of patients with stage II (32% of patients) and only 11% of patients had stage IV disease in their study. Another phase III randomized controlled trial done by Quon et al[29] compared radiotherapy (70Gy) alone to identical radiotherapy plus low-dose weekly cisplatin (20 mg/m^2) in patients with unresectable HNSCC. The complete response rate in the concurrent group was 40% and the median failure-free survival and OS were 7 months and 12 months respectively.

As regards the impact of prognostic factors on treatment outcomes, the present study revealed that poor cell differentiation, advanced T and N stage, advanced overall stage, radiotherapy interruptions and hypopharyngeal primary tumor site are associated with significantly shorter OS in univariate analysis. However in multivariate analysis, only advanced N stage and poor tumor differentiation were significantly associated with shorter OS. In the study done by Krstevska et al[30], T and N stage, overall stage and gross tumor volume were important predictors for short survival.

Results of multivariate analysis in the study done by Rades et al 2008 [11] have also revealed that performance status, stage and interruption during radiotherapy >1week are significant factors affecting survival. Another study done by Rades et al[10] showed that positive Human Papilloma virus status, pre-radiotherapy hemoglobin > 12g/dl, T category (T1-T2) and AJCC stage III were significantly associated with improved survival. The significance of prognostic factors varied between studies. In the study conducted by Stongin et al [31], the primary tumor volume was the best predictor of recurrence and survival in patients with advanced head and neck cancer who received RCT. While in a more recent study, decreased hemoglobin level during RCT and body mass index were among the prognostic factors that predicted outcome in patients with locally advanced head and neck cancer[32].

Regarding acute toxicities in the current study, the rate of grade 3 leucopenia and mucositis was 7% and 30% respectively. This is comparable to the findings of Gupta et al[8] who used the same schedule and reported grade 3 leucopenia and mucositis in 6% and 35% respectively. Homma et al[26] reported a higher rate grade 3 -4 leucopenia and mucositis (26% and 40%, respectively) which may be explained by their use of higher dose of cisplatin (40mg/m^2).

Late toxicities in the present study were mild; grade 2 dysphagia occurred in 6.7% of patients and late skin, laryngeal and mucus membrane toxicity occurred in 15%, 10% and 20% of patients respectively. Quon et al [29] reported a late esophageal toxicity of 9%, skin toxicity in 15%, laryngeal toxicity in 11% and mucus membrane toxicity in 22% of the patients which was comparable to our results.

Machtay et al [20] analyzed previously reported trials of concurrent RCT for locally advanced HNSCC and found that late 43% of patients had a severe late toxicity and concluded that late toxicities are common with RCT. In a phase III, 3-arm, randomized trial comparing conventional radiotherapy to concurrent RCT and accelerated radiotherapy in advanced HNSCC; concurrent RCT was associated with significantly better locoregional control with higher but acceptable acute and late toxicities[33].

CONCLUSION

The results of the current study showed that, in a resource-limited setting, the concurrent administration of weekly cisplatin at a dose of 30mg/m^2 with radical radiotherapy may a feasible therapeutic option for Egyptian patients with non-surgical locoregionally advanced HNSCC.

Acute toxicities were acceptable and late effects in this cohort were low. Improved treatment outcomes were significantly associated with well differentiated tumor, low N stage and interruptions during radiotherapy < 1week. It is important to avoid treatment interruptions to achieve the best treatment results.

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